## REMARKS

### I. Status of Claims

Claims 5 and 44 are amended.

Claims 1- 4, 6-42 and 45 are cancelled.

Claims 5 and 44, 46-47 are being prosecuted.

### II. Interview Summary

An interview was held July 10, 2007. Amendments were proposed which might place the claims in condition for issue. However, the Patent Office believed a new search would be required. An RCE plus arguments were promised by Applicant. A second interview was held on August 31, 2007 and claim amendments were discussed with Examiner Gross and Supervisor Schultz. Applicant appreciates their advice.

### III. Support for Claim Amendments

Support may be found for amendments to claims 5 and 44 in the specification at least in the following locations:

[0014] Here and elsewhere the invention is described as "libraries of pentapeptides enriched in aromatic amino acids," and later in the same para, "It is envisioned that libraries of short D-peptides ranging from 3 to 7 amino acid residues..."

Support for "...a plurality of D-peptides linked to a support..."may be found in the specification, at least in [0018].

p. 4, [0015] 40% or even as many as 50% or more of the D-peptides comprise at least three or more aromatic D-amino acid residues."

"...the remaining amino acids selected from the group consisting of glycine and alanine." [0021] specifies that the non-aromatic amino acids are glycine and alanine.

[0037] "...the D-peptides are suitably constructed or modified to enhance solubility."

p. 13, para 0049 further describes the bead attached peptide library, specifying the use of gly and ala. [0082] phe, tyr, trp, gly and ala.

### IV. The Invention

The goal of the invention is to identify compounds capable of binding to proteins of interest. Methods to identify such compounds and place them in a library are disclosed and claimed in the pending application. The compounds are D-peptides composed of aromatic amino acids.

Peptides in general are not favored as therapeutic agents because of the short half-lives of peptides *in vivo*, because of the actions of proteases and peptidases in degrading the peptides, and rapid peptide excretion through the kidneys. D-configuration aromatic rich peptides are proposed to solve these shortcomings because they are not cleaved by proteases, and the hydrophobic peptides will bind to plasma proteins, mainly albumin, as many hydrophobic drugs do, thus extending their half-lives *in vivo*.

A library of peptides was constructed that only had the aromatic amino acids and, to isolate and to focus on the effects of the aromatic groups, only glycine and alanine were used as spacers. Glycine, having only H atoms on the C alpha carbon, allows for many conformations on either side of the alpha carbon; alanine, having a methyl group off the C alpha carbon, sterically limits the allowed conformations about the C alpha to C carbonyl and C alpha to N bonds, like all the other amino acid R groups, and those phi and psi torsion angles are restricted to what is found in the alpha-helical and beta-strand regions of protein torsion angles. Thus, glycine would allow for some conformations of peptides otherwise restricted by alanine as spacer residue. Also, the conformations of the aromatic rich peptides more likely are mostly restricted because of the aromatic – aromatic R groups non-covalent bonds formed within the peptides.

**V. Neither Pinilla nor Dooley teach all of the claims 5-9 elements and therefore do not anticipate**

Claims 5-8 were reported as anticipated by Pinilla; claims 5-9 were reported as anticipated by Dooley. Only claim 5 is pending.

An anticipating prior art reference should disclose each and every limitation of the claim expressly or inherently. *Akamai Techs. v. Cable & Wireless Internet Servs.*, 344 F.3d 1186, 1192 (Fed. Cir., 2003). To anticipate a claim, a reference must disclose every element of the challenged claim and enable one skilled in the art to make the anticipating subject matter. *PPG Industries, Inc. v. Guardian Industries Corp.*, 75 F.3d 1558, 1566, 37 USPQ2d 1618, 1624 (Fed. Cir. 1996). To serve as an anticipating reference, a reference must enable that which it is asserted to anticipate. *Elan Pharms., Inc. v. Mayo Found.*, 346 F.3d 1051, 1054 (Fed. Cir., 2003). The dispositive question regarding anticipation is whether one skilled in the art would reasonably understand or infer from the prior art reference's teaching that every claim limitation was disclosed in that single reference. *Dayco Prods., Inc. v. Total Containment, Inc.*, 329 F.3d 1358, 1368 (Fed. Cir. 2003) (internal quotation marks and alterations omitted).

Neither Pinilla nor Dooley teach a combinatorial library made up of peptides from 3-7 amino acids in length that only contain aromatic amino acid and, in some lengths, glycine and D-alanine. Nor are the peptides Pinilla or Dooley relate that contain aromatic amino acids soluble. (See Section VI for further discussion of this point.)

**VI. Non-Obviousness of aromatic rich peptides; the claimed peptides are soluble, whereas comparable peptides in Pinilla and Dooley are not**

Claim 5-9 and 43-44 were rejected as obvious over combinations of Dooley, Pinilla, Lam and Lebl. Only claims 5 and 44 are pending.

To properly combine two references to reach a conclusion of obviousness, there must be some teaching, suggestion or inference in either or both of the references, or knowledge generally available to one skilled in the art, which would have led one to combine the relevant teachings of the two references. *Ashland Oil, Inc. v. Delta Resins and Refractories, Inc.* et al. 776 F. 2d 281, (CAFC 1985), Both the suggestion to make the claimed composition or device or carry out the claimed process and the reasonable expectation of success must be founded in the prior art, not in applicant's disclosure. *In re Vaeck* 947 F. 2d 488, (CAFC 1991). Citing references which merely indicate that isolated elements and/or features recited in the claims are known is not a sufficient basis for concluding that the combination of claimed elements would have been obvious, *Ex parte Hiyamizu* 10 PQ. 2d 1393 (BPAI 1988), absent evidence of a motivating force which would impel persons skilled in the art to do what applicant has done. *Ex parte Levengood* 28 PQ. 2d 1300 (BPAI 1993). The references, viewed by themselves and not in retrospect, must suggest doing what applicant has done. *In re Shaffer* 229 F. 2d 476 (CCPA 1956). Obviousness requires a suggestion of all limitations in a claim". *CFMT, Inc. v. Yieldup Int'l Corp.*, 2003 U.S. App. LEXIS 23072 (Fed. Cir. 2003). One cannot simply backtrack from the invention to find a connection to the prior art. Hindsight must be avoided. *W.L. Gore and Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540 (Fed. Cir. 1983). To prevent the use of hindsight based on the invention to defeat patentability of the invention, this court requires the examiner to show a motivation to combine the references that create the case of obviousness. In other words, the examiner must show reasons that the skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed. *In re Rouffet*, 149 F.3d 1350 (Fed. Cir. 1998).

Recently in *KSR Int'l Co. v. Teleflex, Inc.*, No. 04-1350 (U.S. Apr. 30, 2007):

(1) The Court reaffirmed the Graham factors in the determination of obviousness under 35 U.S.C. §103(a). The four factual inquiries under Graham are:

(a) determining the scope and contests of the prior art;

(b) ascertaining the differences between the prior art and the claims in issue;

(c) resolving the level of ordinary skill in the pertinent art; and

(d) evaluating evidence of secondary consideration.

*Graham v. John Deere*, 383 U.S. 1, 17-18, 148 USPQ 459, 467 (1966).

(2) The Court did not totally reject the use of "teaching, suggestion, or motivation" as a factor in the obviousness analysis. Rather, the Court recognized that a showing of "teaching, suggestion, or motivation" to combine the prior art to meet the claimed subject matter could provide a helpful insight in determining whether the claimed subject matter is obvious under 35 U.S.C. §103(a).

(3) The court rejected a rigid application of the "teaching suggestion, or motivation" (TSM) test, which required a showing of some teaching, suggestion, or motivation in the prior art that would lead one of ordinary skill in the art to combine the prior art elements in the manner claimed in the application or patent before holding the claimed subject matter to be obvious.

(4) The Court noted that the analysis supporting a rejection under 35 U.S.C. § 103(a) should be made explicit, and that it was "important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the [prior art] elements" in the manner claimed. The Court specifically stated:

> Often, it will be necessary…to look to interrelated teachings in multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue. To facilitate review, this analysis should be made explicit.

*KSR*, slip op. at 14.

Therefore, in formulating a rejection under 35 U.S.C. §103(a) based upon a combination of prior art elements, it remains necessary to identify the reason why a person of ordinary skill in the art would have combined the prior art elements in the manner claimed.

A person of ordinary skill in the art would not be motivated to combine the 4 publications cited and even if they were, the combination would not teach all claimed elements. Pinilla and Dooley used free peptides, so only those that are soluble in their protein binding assay will be able to bind the protein. In contrast, a great many of the peptides in the present library would not be soluble as free pentapeptides because they are predominantly aromatic amino acids which are hydrophobic (pentapeptides were insoluble in water based buffers). [0037] "D-peptides are suitably constructed or modified so as to enhance solubility." Adding 3 or 4 lysine amino acids to the C-terminal end of the pentapeptides made them soluble in water. Therefore, neither Pinilla or Dooley would be expected to select for hydrophobic peptide sequences as taught in the present application as these would be insoluble in their library. In fact, when they did select sequences with multiple aromatic amino acids they usually contained arginine which could render some sequences soluble in water.

The peptides disclosed in the present application, although very hydrophobic, are soluble in the screening process because they are conjugated to supports such as Tentagel beads through a polyethylene glycol linker.

Page 9, para 0037, relates "In the Examples below, D-peptides…synthesized to include three D-lysine residues to enhance solubility." And in the prior sentence "…the D-peptides are suitably constructed so to enhance solubility." Then the rest of para 0037 further discusses ways to render the peptides soluble.

With regard to the solubility issue: p. 4, para 0018 describes the pentapeptide library being built (synthesized) on TentaGel beads which contain multiple polyoxyethylene (POE) arms terminated by a primary amine group. Standard chemistry is used to attach each amino acid of the library and the split synthesis method yields multiple copies of a single pentapeptide sequence on each bead.

Para 0019 states that the POE arms are water soluble. As known in the art, the aromatic peptides, especially those containing 3 or more aromatic amino acids are insoluble in water based solvents except that they are attached to the POE arms. This allows the peptides to have access to various binding sites of any protein offered to the peptide-bead library.

The present library is made up of only the aromatic amino acids of phe, tyr and trp because their R groups have the unique nature of being able to non-covalently bind to both hydrophilic and hydrophobic R groups of other amino acids, as well as to each other's R groups, and using gly and ala as spacers. An embodiment is pentapeptide sequences. Tetra-, hexa- and hepta- could also have

been used and those variations could be important in certain systems. So the present library has 5 positions and 5 variations of those 5 amino acids at each position, the library consists of only 5 to the 5th power = 3125 different peptides. In order to assure all sequences are in any screening assay, we use about twice the total number of sequences, i.e., 6m250. This corresponds to about 6 mg of the peptide-beads because each bead has a weight of 1ug. This allowed us to practically assess the binding capabilities of the aromatic, D-configuration peptides. The importance of this latter point is seen by contrasting our approach to that used in the Pinilla and Dooley studies. for their initial libraries they had to use either 120 or 400 peptide mixtures in the first screening, each mixture containing about 10 mg per ml) of peptides to achieve a 7nM concentration of each peptide. Thus, in total they had to use somewhere in the range of 1200 to 4000 mg of peptides, and this is for only the first screen. Subsequent screening consumed more peptides. Thus, one can contrast the use of about 6 mg peptide-beads to the grams of peptides needed by the other authors in order to include the aromatic peptide sequences in the specification are important. Regardless of this consideration of amounts of materials, and as described above, Pinilla and Dooley would not be able to identify most if not all of the sequences described here because peptides containing three or more aromatic amino acids would not have been soluble in their system of assay.

Because the aromatic peptides are so hydrophobic, a scientist in this field would predict non-specific hydrophobic type binding to many, if not most or all, proteins. Thus, in screening proteins for binding, a high percentage of beads with attached pentapeptides would be expected to be positive. Furthermore, because of this non-specific, hydrophobic binding, one also would predict that low binding affinities may result of any protein to the peptide-beads. Thus one would have to use relatively high protein concentrations in the screening assays with the peptide-beads in order to see the low affinity type of binding. On the contrary, and as described in the specification, many examples are given of binding using very low concentrations of the proteins, *i.e.*, high affinities were apparently involved in the binding of proteins to particular peptides. Further proof of high affinity binding is in the specification showing the low nM concentrations of the Kd measurements of the ricin and botulinum toxin protein binding to various peptides identified in the screening assays.

Non-obviousness may be shown "by the failure of others." There are a few "carbohydrate" companies that have gone out of business due to lack of success in discovering or making carbohydrate ligands of therapeutic usefulness. The lack of success is largely due to the difficulties in obtaining (by chemical synthesis or isolation from natural sources) of the carbohydrate ligands,

and due to the relatively low binding affinities of carbohydrate ligands with target proteins. Some groups have attempted to circumvent low affinities by making polymers of the carbohydrate ligands but again the chemistry is difficult and the polymers yet lack useful therapeutic value. The aromatic rich peptides circumvent these difficulties for the reasons explained above – and the prediction was demonstrated by the data in the specification. Our data shows that high affinity peptides could be identified for proteins that exhibit much lower binding affinities for their natural carbohydrate ligands.

Furthermore, as described earlier, a relative non-specificity of the bonding interactions of aromatic rich peptides with the proteins tested for binding to the peptides of the aromatic rich peptide library would have been expected. However, the data of the specification supported the specificity of particular aromatic rich peptides binding to particular proteins, and that the binding is characterized as high affinity binding.

Lam or Lebl are added to Pinilla and Dooley to support the obviousness of the rejection, but they do not supply the claim elements missing in Pinilla and Dooley.

**VII. Other issues**

Amendment of claim 5 to "support" should resolve the 112 rejection of "microtiter plate."

Applicants request allowance of the pending claims. Please charge any deficiencies or credit any overpayments to deposit account number 12-0913 with reference to our attorney docket number (45240-105719).

Respectfully submitted,

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Date: Aug 31, 2007

CHDS01 AOM 409212v1